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Background and aims: The cyclin-dependent kinase 4/6 inhibitors (CDKi) are the first line therapy for HER2-metastatic breast cancer. Rate of grade 3/4 CDKi-induced liver injury (CDKi-ILI) in the registry studies was 5–9%. However, real-world data on CDKi-ILI characteristics and, specifically management, is scarce.
Method: Multicenter retrospective study that included all patients who started CDKi between 2018 and 2022 and developed CDKi-ILI ≥2 (CTCAE: AST/ALT >3xULN).
Results: A total of 1716 women were identified (861 palbociclib, 504 ribociclib, 351 abemaciclib) and 85 (4.9%) developed CDKi-ILI: 27 (31.8%) grade-2, 46 (54.1%) grade-3, 12(14.1%) grade-4. Rate of CDKi-ILI was higher ($p < 0.001$) among those treated with ribociclib (8.5%) or abemaciclib (8.0%) than palbociclib (1.6%). No differences were observed in severity (CTCAE: grade≥3: 76.7% ribociclib, 57.1% palbociclib, 60.7% abemaciclib, $p = 0.227$; DILI-IEWG ≥ moderate: 14.0% ribociclib, 7.1% palbociclib, 14.3% abemaciclib, $p = 0.778$). DILI-IEWG ≥ moderate was more frequent in those with increased ALT at baseline ($p = 0.089$), or progressive disease at the time of DILI ($p = 0.015$). Pattern of DILI differed according to the CDKi ($p < 0.001$), with hepatocellular as the most common in patients receiving ribocicib (65.1%) and palbociclib (61.5%), and mixed for abemaciclib (59.3%). Five out of 25 (20%) tested for ANAs presented titers ≥1/80. Half of CDKi-ILI cases presented within the first 3 months of therapy (52.9%), with no difference according to the type of CDKi ($p = 0.521$) or severity ($p = 0.516$). Regarding management, 16 (18.8%) were treated with corticosteroids (CS), especially among those with grade-4 CTCAE ($p < 0.001$) or moderate DILI-IEWG ($p = 0.005$). A tendency to higher rate of CS was observed for those on ribociclib ($p = 0.092$). Median duration of CS was 43 days (IQR 26–57). Liver biopsy was performed in 10 (11.8%) patients, more frequent in patients with grade-4 CTCAE ($p = 0.002$), but similar according to the CDKi ($p = 0.794$). The most frequent findings were presence of eosinophils (90%), bridging necrosis (40%), cholestasis (40%), interphase hepatitis (30%), lymphocytic/lymphoplasmacytic infiltrate (50%). After a median of 36 days (IQR, 16–80), 70 (82.4%) patients were rechallenged, rate lower in case of prior DILI-IEWG ≥moderate ($p = 0.022$), but similar regardless of the initial CDKi ($p = 0.287$) or CTCAE ($p = 0.507$). Change on the CDKi was more common among those previously treated with ribociclib ($p = 0.031$), presenting with hepatocellular pattern ($p = 0.039$) and grade 3/4 CTCAE ($p < 0.001$). Recurrence of CDKi-ILI was observed in 19/70 (27.1%) patients, all of them mild.
Conclusion: CDKi-ILI is common, especially within the first months of therapy with ribociclib or abemaciclib. Management of CDKi-ILI is heterogeneous and its standardization a necessity in view of the recent approval of ribociclib and abemaciclib as adjuvant therapy.

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Corticosteroids are ineffective in individuals with severe alcohol-associated hepatitis and early spontaneous improvement: a multicenter randomized controlled trial

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Background and aims: Severe alcohol-associated hepatitis (AH) is a life-threatening disease for which corticosteroid therapy is recommended in the absence of contraindication. A significant proportion of patients with severe AH have a spontaneous serum bilirubin decrease early after admission. Our aim was to determine whether corticosteroid therapy is more effective than placebo in individuals with severe AH and early spontaneous improvement.
Method: In this multicenter, randomized, controlled trial conducted between February 2018 and May 2024 in 10 Belgian hospitals, patients aged 18 or older, who were heavy drinkers, with recent onset of jaundice, with a biopsy-proven severe AH (mDF ≥ 32 at admission), and with a spontaneous early improvement (i.e. serum bilirubin level decrease > 10% at day 5–10 after admission) were randomized to either corticosteroids (CS) (methylprednisolone 32 mg/d) or placebo (P) for 28 days. Primary endpoint was to compare 3-month mortality rate between both groups of treatment. Secondary endpoints were to compare 1-month mortality rate and infection rate during study period between both groups.
Results: A total of 69 patients were randomized, 38 in the corticosteroid group and 31 in the placebo group. Baseline characteristics were not significantly different between the two groups (CS vs P) for age (52 ± 8 vs. 51 ± 10), male gender (76% vs. 63%), total bilirubin (7.4[5.1–10.8] vs. 9.3[6.0–17.6] mg/dL), INR (1.64 [1.48–1.80] vs 1.70 [1.48–1.98]), mDF at admission (44[37–57] vs. 45[40–58]) and MELD score (21[19–23] vs 21[19–24]). Decrease in bilirubin level between admission and screening was not different between both groups (31 ± 15% vs 27 ± 11%). Lille score at day 7 of treatment was 0.18 [0.07–0.30] and 0.18 [0.07–0.40] in CS and P group, respectively ($p > 0.9$). At 3 months, the probability of survival was not different between both groups (83[72–96] vs 82[69–98] % in CS and P groups respectively, $p = 0.88$). There was no difference in the probability of 1-month survival between CS and P groups (95[88–100] vs 94[85–100] %, $p = 0.85$). Probability of infection during the study period was 48% in the CS group and 36% in the P group ($p = 0.41$). Age and Lille score were significantly associated with 3-month survival. The study was prematurely interrupted due to a low recruitment rate.
Conclusion: The present study failed to identify any benefit from corticosteroid therapy in patients with severe AH and early decrease in bilirubin level after admission. Even if the number of included patients initially planned was not reached, it is unlikely that corticosteroids provide a survival benefit when bilirubin level spontaneously decreases by at least 10%. Waiting five days after admission before deciding to start steroids seems to be a reasonable strategy.